

Remarks

Applicants appreciate the Examiner's acknowledgement that claims 40-44 are patentable over the prior art of record. Applicants also appreciate the Examiner's withdrawal of the following rejections: (1) the rejection of claims 43 and 44 under 35 U.S.C. § 112, second paragraph, (2) the rejection of claims 46 and 47 under 35 U.S.C. § 102(b) as anticipated by Cruz *et al.*, and (3) the rejection of claims 40-49 under 35 U.S.C. § 112, second paragraph.

The Amendments

New claims 63-66 recite deletion mutations. Deletion mutations are disclosed on page 9, lines 1-2. New claims 65 and 66 recite steps by which the deletion mutations can be made. These steps are disclosed *inter alia* on page 6, line 15, to page 7, line 28.

The amendments do not add new matter or require a new search.

The Rejection of Claims 47, 55, and 56 Under 35 U.S.C. § 102(b)

Claims 47, 55, and 56 stand rejected under 35 U.S.C. § 102(b) as anticipated by Ricketts *et al.*, *Third International Veterinary Immunology Symposium Budapest, Hungary*, abstract PS7.19, August 17-20, 1992 (“Ricketts”). Claims 47, 55, and 56 have been canceled, mooting the rejection.

The Rejection of Claims 46-49 Under 35 U.S.C. § 102(b)

Claims 46-49 stand rejected under 35 U.S.C. § 102(b) as anticipated by Chidambaram *et al.*, B-143, May 1992 (“Chidambaram I”), “as evidenced by” Chidambaram *et al.*, *Inf. Immun.*

95, 1027-32, 1995 ("Chidambaram II"). Claims 46 and 47 have been canceled. Applicants respectfully traverse the rejection of claims 48 and 49.

Independent claims 48 and 49 are directed to vaccines to induce protective immunity against *Pasteurella haemolytica* infection. The vaccines comprise an isolated *Pasteurella haemolytica* bacterium comprising a mutation that attenuates the bacterium. The mutation is in a leukotoxin B gene (claim 48) or a leukotoxin D gene (claim 49).

Chidambaram I is cited as inherently disclosing "two mutant strains . . . that were negative for leukotoxin production . . ." Office Action at page 14, second full paragraph. Mutations in the leukotoxin B or D genes would not be responsible for such a phenotype. The leukotoxin B and D genes are involved in the secretion of leukotoxin, not in its production. See Highlander *et al.*, *J. Bacteriol.* 172, 2343-50, 1990 (copy provided with attached Supplemental Information Disclosure Statement); Davies *et al.*, *J. Bacteriol.* 184, 266-77, 2002 (cited in the Office Action).

Chidambaram I also does not anticipate new claims 63-66, which recite deletion mutations in the leukotoxin B (claims 63 and 65) or D (claims 64 and 66) genes. The mutants disclosed in Chidambaram I were obtained by nitrosoguanidine mutagenesis (line 1). Nitrosoguanidine is an alkylating agent. See Hashimoto *et al.*, *Clin Cancer Res.* 1995 Apr;1(4):369-76 (abstract; Attachment 1); this mutagen does not create deletion mutations. Thus, Chidambaram I contains no disclosure whatsoever to indicate that the disclosed mutants comprise a deletion mutation in the leuktoxin B or D genes, as recited in claims 63-66.

Chidambaram II is cited as providing extrinsic evidence that Chidambaram I inherently anticipates the subject matter of claims 48 and 49. Extrinsic evidence cited to show inherency must meet a stringent standard:

To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

Continental Can Co. USA, Inc. v. Monsanto Co., 984 F.2d 1264, 1268; 20 U.S.P.Q.2d (BNA) 1746, 1749-50 (Fed. Cir. 1991). Chidambaram II does not meet this standard and so does not provide legally sufficient evidence to show that Chidambaram I inherently anticipates claims 48 and 49.

First, to provide extrinsic evidence that Chidambaram I anticipates claims 48 and 49, it should be clear that Chidambaram II discloses the same mutant strains as Chidambaram I. This does not appear to be the case. Although Chidambaram II does disclose “[t]wo mutants of *Pasteurella haemolytica* A1 that do not produce leukotoxin” (abstract), there is no evidence whatsoever that the mutants disclosed in Chidambaram II are the same mutants disclosed in Chidambaram I. In fact, Chidambaram II (published in 1995) does not even cite the Chidambaram I reference (published in 1992). See the reference list on pages 1031-32.

Second, even if *arguendo* the Chidambaram II and Chidambaram I mutants ~~were~~ identical, Chidambaram II does not establish that Chidambaram I discloses mutations in the leukotoxin B or D genes, much less deletion mutations in those genes. The Office Action cites a passage at page 1030, col. 2 as teaching an “overall genomic arrangement [sic; rearrangement] of the leukotoxin operon, which introduced mutations into leukotoxin genes C, D and B.” Chidambaram II does not contain the asserted teaching. The cited passage, which begins at page 1030, col. 1, second full paragraph, discloses the results of restriction enzyme digests using enzymes that “cut the *P. haemolytica* genome into only about seven fragments.” These results

merely demonstrate that the mutant identified as "59B0072" contained some genomic rearrangements with respect to the parent genome. But continued reading of this section of Chidambaram II reveals that the genomic rearrangements are not in the leukotoxin operon:

We next examined the fragment that contains the lkt locus to determine if the leukotoxin-negative phenotype was due to a large deletion. The pulsed-field gel was blotted and probed with a cosmid that contains a 20-kb insert that includes the entire lkt locus. As shown in Fig. 4, the fragment that contains the lkt locus was the same in the parent and the two mutant strains, despite the differences in restriction fragments between 59B0072 and the other two strains. Also shown in Fig. 4 is the pattern from another *P. haemolytica* strain, PHL101, from which we previously cloned the lkt locus. This strain also showed differences from the parental strain used in this study in its genomic restriction pattern. It is not known whether the differences in the gel patterns are due to plasmids as well as restriction fragment length polymorphisms. It should be noted that differences such as those seen between PHL101 and 59B049 are common when bacteria are examined by pulsed-field gel electrophoresis. However, by Southern blot it is apparent that the same-sized fragment contains the lkt locus in PHL101. Thus, we conclude that despite the different total genomic patterns in these four strains, there is no gross rearrangement in the lkt region in the two mutants.

To look more closely at this region, digestions were performed with restriction enzymes that cut more frequently and the resulting blots were probed with the same cosmid. As shown in Fig. 5, the same pattern was seen for the parent and the two mutants. Fig. 6 shows the restriction map of this region, indicating the fragments detected in the blot shown in Fig. 5. It is clear that no gross rearrangement is present in the mutants.

Page 1031, col. 1, lines 1-28, internal references omitted. Thus, contrary to the Office Action's assertion, Chidambaram II does not teach an "overall genomic arrangement [sic; rearrangement] of the leukotoxin operon, which introduced mutations into leukotoxin genes C, D and B."

Even if *arguendo* Chidambaram I and II disclosed the same mutant strains, the defects of Chidambaram II as extrinsic evidence to establish inherent anticipation by Chidambaram I are

manifest. As explained above, there is no evidence that the mutant strains disclosed in Chidambaram I and II are the same. Thus, Chidambaram II does not provide legally sufficient evidence that Chidambaram I inherently anticipates the subject matter of claims 48 and 49. Without extrinsic evidence to show that Chidambaram I inherently discloses the bacteria recited in claims 48 and 49, Chidambaram I does not satisfy the first requirement of a reference under 35 U.S.C. § 102(b).

Applicants respectfully request the withdrawal of the rejection.

The Rejection of Claims 46-49 and 51-62 Under 35 U.S.C. § 112, first paragraph

Claims 46-49 and 51-62 stand rejected under 35 U.S.C. § 112, first paragraph, as not enabled. Claims 46, 47, and 51-56 have been canceled. Applicants respectfully traverse the rejection of claims 48, 49, and 57-62.

To support a finding of non-enablement, the U.S. Patent and Trademark Office must establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d (BNA) 1510, 1513 (Fed. Cir. 1993). The Office must not only explain why it doubts the teachings of the specification, but also must support its assertions “with acceptable evidence or reasoning which is inconsistent with the contested statement.” *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. (BNA) 367, 370 (C.C.P.A. 1971). The Office has not met its burden of providing acceptable evidence or reasoning to support a *prima facie* case of non-enablement.

The enablement rejection was maintained from the last Office Action mailed August 8, 2002 (Paper No. 16). That Office Action attempted to meet the burden of making a *prima facie* case of non-enablement by citing numerous references asserted to show that “vaccines

comprising *Pasteurella haemolytica* are unpredictable in methods of treating or preventing infection." Paper No. 16, page 11, first full paragraph. In response, Applicants explained that the cited documents did not provide the acceptable evidence or reasoning required to establish a *prima facie* case of non-enablement because none of them teaches the type of vaccine disclosed and claimed in the present application. In fact, all the vaccines disclosed in the cited prior art are quite different from the vaccines recited in the pending claims. See pages 8-9 of the response filed November 8, 2002.

The present Office Action responds to this argument by agreeing that the prior art does not disclose the type of vaccines claimed:

Clearly in view of the cited vaccine art provided in Applicant's response dated November 8, 2002 (pages 8-9) leukotoxin mutant *Pasteurella haemolytica* vaccines are not generally known in the art. . . [T]he knowledge that is generally known in the art does not define any *Pasteurella haemolytica* vaccines with mutations in a leukotoxin gene (A, B, C or D open reading frames).

Paper No. 21 at page 3, last paragraph. Thus, the present Office Action merely acknowledges that the subject matter of claims 48, 49, and 57-62 is novel over the prior art. Acknowledgement of novelty, however, is not a legally sufficient argument to support a *prima facie* case of non-enablement.

In the present Office Action, the U.S. Patent and Trademark Office cites yet another lengthy list of references in its continued attempt to show that claims 48, 49, and 57-62 are not enabled. For example, Chidambaram II is cited as teaching that "[s]ince no mutagenesis procedure had been published previously for *P. haemolytica*, it was first necessary to establish a mutagenesis protocol. (See page 1028, col. 2, paragraph 4)." Paper No. 21 at page 4, first paragraph. Chidambaram II, however, is not prior art to the present application. Chidambaram

II was published in 1995, whereas the priority date of the present application is December 6, 1993.¹ The present application teaches how to obtain *P. haemolytica* mutants, as discussed in the response filed November 8, 2002 at pages 4-5. These teachings are present in the parent specification filed December 6, 1993. The fact that the authors of Chidambaram II were apparently unaware of the teachings in Applicants' 1993 specification does not negate the enablement provided in the parent application.

The present Office Action also cites Chidambaram II as teaching that "genetic mapping is not yet possible for *P. haemolytica* (see page 1030, col. 1, paragraph 3)." Paper No. 21 at page 4, end of first paragraph. It is not clear what is meant by "genetic mapping" or why this statement in Chidambaram II provides evidence that claims 48, 49, and 57-62 are not enabled. Leukotoxin genes had been studied long before the present application was filed and before Chidambaram II was published. See, for example, Lo *et al.*, "Cloning and expression of the leukotoxin gene of *Pasteurella haemolytica* A1 in *Escherichia coli* K-12," *Infect. Immun.* 50, 667-71, 1985 (copy provided with attached Supplemental Information Disclosure Statement); Lo *et al.*, "Nucleotide sequence of the leukotoxin genes of *Pasteurella haemolytica* A1," *Infect. Immun.* 55, 1987-96, 1987 (copy provided with attached Supplemental Information Disclosure Statement); Highlander SK, Chidambaram M, Engler MJ, Weinstock GM, "DNA sequence of the *Pasteurella haemolytica* leukotoxin gene cluster," *DNA* 8, 15-28, 1989 (of record); and Strathdee & Lo, "Cloning, nucleotide sequence, and characterization of genes encoding the secretion function of the *Pasteurella haemolytica* leukotoxin determinant," *J. Bacteriol.* 171, 916-28, 1989 (copy provided with attached Supplemental Information Disclosure Statement).

¹ The present application is a continuation of Serial No. 08/643,299 filed May 8, 1996, which is a division of Serial No. 08/162,392, filed December 6, 1993.

The Office also frets about the possibility that mutagens may induce prophage induction in *P. haemolytica*. Paper No. 21 at page 4, first paragraph. This is a red herring. Mutagen induction of prophage would possibly occur only if the *P. haemolytica* containing the prophage were directly exposed to the mutagen. The present specification, however, teaches a method for obtaining *P. haemolytica* mutants that does not involve direct mutagenesis of *P. haemolytica* bacteria. Instead, DNA is mutagenized *in vitro*, and then the mutagenized DNA is introduced into *P. haemolytica*, thereby eliminating the possibility of mutagen-induced prophage induction. See Example 6.

The Office Action also cites Potter (U.S. Patent 5,871,750, which claims priority to an application filed April 7, 1989), Martin *et al.* (*Can. J. Comp. Med.* 44, 1-10, 1980), Weekley *et al.* (July 1993), Kiorpis *et al.* (1991), Summit *et al.* (*Biotechnology News*, 1990), Gentry *et al.* (April 1988) as “evidence” that, despite the enabling teachings in the specification, the claimed vaccines would not work as taught. The mere fact that the Office can identify references that attest to a lack of a vaccine effective against *P. haemolytica* infection prior to the invention does not undermine the present specification’s enabling teachings of such a vaccine. The cited prior art in fact underscores the inventiveness of the claimed vaccines.

The Office has not met its burden of providing acceptable evidence or reasoning to support a *prima facie* case of non-enablement and of giving proper weight to the evidence of record. Instead, the Office has focused on irrelevant evidence and has not given proper weight to the relevant evidence of record.

A *prima facie* case of non-enablement has not been made. Applicants respectfully request withdrawal of the rejection.

The Rejection of Claims 46-49 and 51-62 Under 35 U.S.C. § 112, first paragraph

Claims 46-49 and 51-62 stand rejected under 35 U.S.C. § 112, first paragraph, as not sufficiently described in the specification. Claims 46, 47, and 51-56 have been canceled. Applicants respectfully traverse the rejection of claims 48, 49, and 57-62.

The U.S. Patent and Trademark Office continues to use a scattershot approach to support its written description rejection. The Office Action contains numerous statements asserted to show that the claimed invention is not sufficiently described. None of these statements focuses on the correct inquiry: would the present specification have sufficiently described the claimed invention to one skilled in the art?

First, the Office Action faults the specification for not disclosing the sequence of neuraminidase. Page 9, lines 12-14. None of the pending claims recites neuraminidase; it is irrelevant whether the sequence of this protein was disclosed when the specification was filed.

Second, the Office Action faults the sentence at page 7, lines 11-12 as not disclosing any specific sites for mutagenesis of the leukotoxin genes. Page 10, lines 1-2. Again, none of the pending claims recites any specific sites for mutagenesis of a leukotoxin gene. The sentence at page 7, lines 11-12 reads, “Other genes in which mutations may be desirable are genes in the leukotoxin operon (C, A, B, D) and neuraminidase.” This sentence provides explicit support for the subject matter of independent claims 48 and 49: isolated *Pasteurella haemolytica* bacteria that comprise a mutation in a leukotoxin B or D gene. Admittedly it does not provide support for specific sites for mutagenesis, but none are claimed.

Third, the Office Action cites two post-priority date publications by Davies *et al.* (*J. Bacteriol.* 183, 1394-1403, 2001; *J. Bacteriol.* 184, 266-67, 2002) as evidence that “the leukotoxin operon evidences many structural allelic variations . . . which are highly polymorphic

...." Page 10, last paragraph. The Office Action also states that "[t]he highly pleomorphic [sic; polymorphic] nature of leukotoxin genes due to many allelic variations was not well known at the time of filing, and the claims are not limited to the sequence, species or strain for which the sequences were known and there is no guidance to utilize any specific sequence or strain(s) in the production of claim [sic; claimed] mutants." Paragraph bridging pages 10 and 11. It is not clear how the Davies publications support the written description rejection. As evidenced by the explicit disclosure in the specification, Applicants were in possession of the invention of claims 47, 48, and 57-62: vaccines comprising a *P. haemolytica* bacterium comprising an attenuating mutation in a leukotoxin B or D gene. The fact that leukotoxin genes are now known to be polymorphic does not undermine the specification's explicit support for the claimed bacteria. Claims 48, 49, and 57-62 are directed to *vaccines*, not to *genes*.

Fourth, the Office continues to rely on Highlander (*DNA 8*, 15-28,1989), stating that "no vaccines [sic; vaccine] strains of *P. haemolytica* mutants are disclosed in Highlander." Page 12, lines 1-2. What Highlander does or does not teach is of no relevance in determining whether the present specification describes the invention of claims 48, 49, and 57-62. The written description requirement of 35 U.S.C. § 112, first paragraph states that "*[t]he specification* shall contain a written description of the invention" (emphasis added). It is the present specification that must satisfy the written description requirement, not Highlander.

Fifth, the Office Action faults the Declaration filed February 13, 2001 because it "set[s] forth data for a species of mutant strain of *P. haemolytica*, which was not specifically suggested or taught, the data in the Declaration being asserted as showing enablement for the generically claimed vaccines of leukotoxin mutant strains of *Pasteurella haemolytica*." Page 12, second full paragraph. As acknowledged in the Office Action, the Declaration was submitted in response to

the enablement rejection; the fact that the Declaration contains data for a species not specifically disclosed has no bearing on whether the specification meets the written description requirement for the pending *generic* claims. Applicants do not claim the species described in the declaration.

Sixth, the Office continues to cite *Fiers v. Revel*, *Amgen v. Chugai*, and *Fiddes v. Baird*. The cited cases address written description of claimed novel genes. Claims 48, 49, and 57-62 are not directed to novel *genes*, but to *vaccines* comprising a *P. haemolytica* bacterium with a particular characteristic, *i.e.*, a mutation in one of two known genes (leukotoxin B or D) that attenuates the bacterium. A specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. (BNA) 81, 94 (Fed. Cir. 1986). Thus, the present specification need not disclose the sequences of the leukotoxin genes to provide a written description of the claimed vaccines.

Seventh, the Office Action asserts that “[o]ne cannot describe what one has not conceived.” Page 13, line 1. Applicants conceived of vaccines to induce protective immunity against *Pasteurella haemolytica* infection. The vaccines comprise an isolated *Pasteurella haemolytica* bacterium which comprises a mutation in a leukotoxin B or D gene, wherein the mutation attenuates the bacterium. This is exactly what is claimed and is exactly what is disclosed. The Office Action has not provided *any* evidence that Applicants failed to conceive of the invention.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,
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